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Exercise capacity and quadriceps muscle metabolism following training in subjects with COPD

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Summary The aim of the study was to determine whether 16 sessions of exercise training, completed twice weekly, alters exercise capacity, quadriceps muscle metabolism, cross-sectional area (CSA) and strength in subjects with chronic obstructive pulmonary disease (COPD). We studied (a) 10 COPD subjects (mean age $\pm$ SEM = 71 $\pm$ 2 years; $FEV_1 = 0.99 \pm 0.1$ L) before and after 16 sessions of exercise training, and (b) 10 healthy subjects (age = 68 $\pm$ 3 years). The COPD subjects underwent an incremental peak exercise test using a cycle ergometer and a 6-min walk test: both improved following exercise training ($P < 0.05$). Magnetic resonance spectroscopy measurements, in quadriceps muscle, of post-exercise phosphocreatinine (PCr) recovery kinetics were used to assess mitochondrial function in vivo: in the COPD subjects pre-training this was 19 $\pm$ 8% lower than in healthy subjects ($P = 0.03$), but a 38 $\pm$ 12% increase was seen in the COPD subjects following training ($P = 0.003$). Magnetic resonance imaging was used to assess quadriceps CSA: after training in the COPD subjects this showed a 7 $\pm$ 2% increase ($P = 0.03$). Quadriceps strength, measured by the best of five maximum voluntary contractions, also showed a 32 $\pm$ 11% increase in the COPD subjects ($P = 0.007$). Sixteen sessions of exercise

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training, performed twice weekly, increased exercise capacity as well as quadriceps mitochondrial capacity, CSA and strength in the subjects with COPD.

Introduction

Skeletal muscle dysfunction has been proposed to be a primary determinant of reduced exercise capacity in subjects with chronic obstructive pulmonary disease (COPD).[1] A number of studies have shown a reduction in muscle endurance,[2–6] strength[7–9] and muscle atrophy[3,10,11] in subjects with COPD.

The cause of skeletal muscle dysfunction and the extent to which it occurs in all COPD subjects is currently under debate. Physical inactivity and consequent deconditioning may be an important cause, and so exercise training may be an important preventive and therapeutic strategy. Physiological benefits from moderate-to-high-intensity exercise training, performed 3–5 times weekly for 8–12 weeks, have been shown in subjects with moderate to severe COPD[12–14] including an increase in muscle oxidative enzymes.[13] No studies were identified that have examined both muscle metabolism and exercise capacity following twice weekly, supervised exercise training.

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is a non-invasive method of assessing skeletal muscle metabolism at rest, during exercise and in recovery. One study[15] has used ^{31}P-MRS to examine the effect of cycle training performed five times weekly for 8 weeks on quadriceps muscle metabolism in moderate COPD, reporting a longer than normal half-time of post-exercise phosphocreatine recovery (PCr $t_{1/2}$) in the COPD subjects prior to training, suggestive of a defect of muscle oxidative capacity, which improved after training.

The primary aim of this study was to examine the effect of 16 sessions of an endurance and strength training program, performed twice weekly, on exercise capacity, quadriceps mitochondrial capacity, and quadriceps cross-sectional area (CSA) and strength in subjects with COPD. The hypothesis was that the exercise training would increase exercise capacity as well as quadriceps mitochondrial capacity, CSA and strength in the subjects with COPD.

Methods

Subjects

Ten subjects diagnosed with COPD (6 male, 4 female) were recruited from the pulmonary rehabilitation program at Royal Prince Alfred Hospital (RPAH), Australia. Subjects were included if they had COPD Stage II and Stage III as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards[16] and excluded if they had previously undergone pulmonary rehabilitation, required oxygen therapy, were still smoking or suffered from claustrophobia.

Ten healthy, age-matched, control subjects (5 male, 5 female) were recruited from the general community. These subjects had no respiratory history and were sedentary, assessed by the physical activity questionnaire[17] in which sedentary physical activity level was defined as expending $<10\%$ of daily energy expenditure in the performance of moderate-to-high-intensity activities (i.e. a resting metabolic equivalent level >4 METS).[18]

All subjects were questioned about their capacity to enter a magnetic field. Standard magnetic resonance exclusions applied.

Informed, written consent was obtained from all subjects, and the study was approved by the Ethics Review Committee (RPAH zone) of the Sydney South West Area Health Service.

All COPD subjects had testing performed at baseline and following 8 weeks exercise training. All healthy subjects had testing performed at baseline only.

Muscle tests

Both magnetic resonance imaging (MRI) and ^{31}P-MRS were performed. The same protocol was used on all subjects. This protocol has been previously described by this group.[19] Subjects lay prone on a custom-built rig positioned inside a Philips 1.5 T Gyroscan Intera magnet (Philips Medical Systems, Best, The Netherlands). The right thigh was strapped to the rig (Fig. 1) with the P-100 pulse-receive coil (Philips Medical Systems, Best, The Netherlands) positioned under the right quadriceps muscle. The right knee was flexed to 30° with the lower leg positioned on a force platform which was equipped with an electronic load cell (PT-100 PT electronics, Auckland NZ) to evaluate force production.

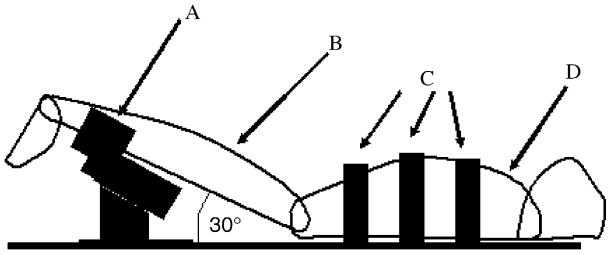

Figure 1 Schematic of leg positioning on the rig. (A) force platform, (B) lower leg, (C) straps, (D) thigh.

Magnetic resonance imaging

Images of the right quadriceps muscle were taken to assess CSA. Two transverse stacks of T2 weighted images (6 mm thick–30 mm gap) were collected. The area of the quadriceps muscle group was analysed manually using the Philips Easy Vision software (Philips Medical Systems, Best, The Netherlands). The CSA was taken as the maximal uncorrected area from review of all the single images from that subject.

Magnetic resonance spectroscopy

An adiabatic pulse sequence was used to collect eight unlocalised ^{31}P spectra (TR = 1500 ms), summed to assess resting metabolic state. Spectra were Fourier transformed and analysed for [PCr], adenosine triphosphate ([ATP]), adenosine diphosphate [ADP], and inorganic phosphate ([Pi]) using the Java-based magnetic resonance user interface (jMRUI version 2.0, EU Project).[20] The chemical shift between [PCr] and [Pi] was used to measure muscle acidity (pH).[21]

Each subject performed five maximum voluntary contractions of the right quadriceps muscle with 15 s of rest between contractions, taking the highest value as the maximum voluntary contraction (MVC). The exercise protocol consisted of pushing against the force platform at 60% MVC for 3 s followed by 1 s relaxation. Visual force feedback was provided using a custom-built display unit combined with a light metronome to ensure correct timing of contraction and relaxation. The exercise cycle was repeated for 3 min (45 cycles), after which the subject was rested for 7 min. Spectra were collected every 4 s during exercise and recovery, 150 in all (TR 4000 ms), and analysed as for the resting spectra. In the COPD subjects, the same relative workload (i.e. 60% MVC) was used post-training following re-measurement of the MVC.

Muscle oxidative function was assessed from the recovery kinetics of PCr, fitting a least-squares monoexponential time-function to determine the halftime ($t_{1/2}$) and initial rate of PCr resynthesis. The initial rate is a measure of the absolute end-exercise rate of oxidative ATP synthesis, and the halftime is an inverse measure of mitochondrial capacity (independent of the degree of PCr depletion), i.e. the maximum rate of oxidative ATP synthesis[22] if appropriate allowance is made for pH change during exercise. We exploited the invariant near-linear relationship between PCr $t_{1/2}$ and end-exercise pH[23,24] first to establish group differences in mitochondrial function, and then to calculate for each subject the ratio of the PCr $t_{1/2}$ predicted from the end-exercise pH to that observed; this is a robust measure of the mitochondrial capacity in a subject relative to that on average in the controls.

Lung function tests

In the COPD subjects, measurements of spirometry and lung volumes were performed (Sensormedics Vmax 20 and Sensormedics V6200 Autobox Body Plethysmograph respectively; Sensormedics Corporation, CA) and compared to predicted normal values for spirometry[25] and for lung volumes.[26] In the healthy subjects, measurements of spirometry were performed using a hot-wire anemometer (Minato Autospiro AS-500; Minato Medical Science, Osaka, Japan).

Exercise tests

Exercise tests were only performed in the COPD subjects. An incremental symptom-limited cycle test was performed on an electrically braked bicycle ergometer (Sensormedics 800 Computerised Ergometer, Sensormedics Corporation, CA). Each subject breathed through a calibrated mass flow sensor with expired gas sampled on a breath-by-breath basis (Vmax 29 Cardiopulmonary Exercise Testing Instrument; Sensormedics Corporation, California, USA) so that oxygen consumption V_{O_2}, carbon dioxide production, minute ventilation (V_E), tidal volume and breathing frequency could be determined. The peak V_{O_2} and peak workload from this test were compared to the predicted normal values.[27] Heart rate (HR) and percent oxygen saturation were obtained with a finger probe attached to a pulse oximeter (N200: Nellcor, Hayward CA). Each subject scored their dyspnea and rate of perceived exertion on a modified Borg scale reading 0 (''nothing at all'') to 10 (''maximal''). Peak values were compared before and after exercise training.

A 6 min walk test was conducted in accordance with a standardised protocol.[28] All subjects completed two walks separated by 30 min rest. Each

subject was asked to walk as far as they could in 6 min up and down a 12 m track which was marked out by tape. Standardised encouragement was given throughout. The better 6 min walk distance (6MWD) was used in the data analysis.

Exercise training

Each session of exercise training consisted of supervised leg cycling, walking, and leg strength training performed twice per week for 8 weeks. Sixteen sessions of exercise were required to be completed prior to final testing. The intensity of cycle exercise was set from the peak leg cycle exercise test. The cycle training initially consisted of a 5-min warm-up at 40% peak work, 5–10 min exercise at 60% peak work and a 5-min cool-down at 40% peak work. The intensity and duration of cycling was progressed as able. The intensity was increased up to 80% peak workload by week 8 and the duration was progressed to 20 min by week 4 and to 30 min by week 8. The intensity of walking was set at 80% of the walking speed calculated from the initial 6 min walk test, for 20 min initially and progressed to 30 min by week 8.

Strength training for the quadriceps was performed on a leg extension machine. Training consisted of two sets of 8–10 repetitions at 70% of the one repetition maximum (1RM). This was progressed, if able, up to three sets of 10 repetitions by week 4 and up to three sets of 10 repetitions at 80% of 1RM by week 8.

Statistical analysis

Statistical analysis used StatView (Version 4.57 1992–1996, Abacus Concepts Inc., Berkeley, California) and StatsDirect (v. 2.4.1 http://www.statsdirect.com/). All data are presented as mean ± standard error of the mean (SEM). Variables were compared between groups using an unpaired *t*-test and within the COPD subjects from pre- to post-training using a paired *t*-test. Grouped linear regression was used to assess the relationship of PCr $t_{1/2}$ to end-exercise pH, and simple linear regression to back-predict PCr $t_{1/2}$ using the pH-$t_{1/2}$ relationship in controls. Linear regression was used to assess the relationship between change in exercise capacity and mitochondrial capacity in the subjects with COPD. A *P*-value of <0.05 was taken to be significant.

Results

Mean anthropometric data and lung function results are presented in Table 1. Lung function in the COPD subjects was significantly reduced compared to the healthy subjects. The mean time to complete 16 sessions of exercise training in the COPD subjects was 9.7 ± 0.5 weeks. By the end of the 16 sessions, 90% of subjects had achieved the required walking protocol, 30% had achieved the required cycling protocol (of the remainder: 40% of subjects were cycling for 20 min at 60% peak work and 30% were cycling for 30 min at 60% peak work), and all subjects were performing strength training for 3 sets of 10 repetitions at 70–80% 1RM.

Results of quadriceps muscle testing are presented in Table 2. There was a significant increase in the initial rate of PCr resynthesis from pre- to post-training in the COPD subjects. As PCr depletion was also significantly greater from pre- to post-training, the PCr $t_{1/2}$ did not differ. The relationship between PCr $t_{1/2}$ and end-exercise pH had a statistically indistinguishable slope in all three groups, with a significant vertical separation between COPD subjects pre-training and controls, and between COPD subjects pre- and post-training (both $P<0.01$) (Fig. 2A). Thus for a given pH change, PCr $t_{1/2}$ was higher (i.e. mitochondrial

Table 1 Anthropometric and lung function data in the healthy control subjects ($n = 10$) and in the COPD subjects ($n = 10$) before and after exercise training (ET)

	Healthy control baseline	COPD	
		Pre-ET	Post-ET
Age (yr)	68 ± 3	71 ± 2	71 ± 2
BMI (kg/m^2)	25 ± 2	26 ± 1	26 ± 1
FEV_1 (L)	2.4 ± 0.2	0.99 ± 0.1*	1.1 ± 0.1
% pred	103 ± 4	42 ± 5*	44 ± 6
FVC (L)	3.0 ± 0.3	2.3 ± 0.2*	2.3 ± 0.1
% pred	93 ± 4	67 ± 5*	69 ± 3
TLC (L)		6.3 ± 0.5	6.5 ± 0.5
% pred		120 ± 6	121 ± 5
FRC (L)		4.5 ± 0.4	4.5 ± 0.4
% pred		150 ± 14	150 ± 12
RV (L)		4.0 ± 0.4	4.0 ± 0.4
% pred		188 ± 16	189 ± 15

Data are mean ± SEM. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; FRC: forced residual capacity; RV: residual volume.

*Significantly different from healthy control group ($P<0.05$).

Table 2 Results of quadriceps muscle testing in the healthy control subjects ($n = 10$) and in the COPD subjects ($n = 10$) before and after exercise training (ET)

	Healthy control baseline	COPD	
		Pre-ET	Post-ET mean difference (95% CI)
Resting			
Quads CSA, cm^2	47±5	46±2	49±3† 3 (3 to 6)
Resting pH	7.04±0.01	7.04±0.01	7.06±0.01 0.02 (−0.004 to 0.05)
Resting [PCr], mM	33±1	34±1	34±1 0.4 (−4 to 5)
Exercise			
MVC, kg	25±2	24±3	30±3† 6 (2 to 9)
End-exercise [PCr] fall, mM	11±2	13±2	16±1† 3 (0.9 to 5)
End-exercise pH change	−0.26±0.07	−0.24±0.05	−0.40±0.09 −0.2 (−0.4 to 0.01)
End-exercise ADP, μM	33±3	35±6	35±6 −1 (−17 to 14)
Recovery			
Initial [PCr] resynthesis rate, mM/min	13±1	12±1	19±2† 6 (2 to 11)
PCr $t_{1/2}$, s	35±3	45±4	39±5 −5 (−15 to 4)
Predicted/observed PCr $t_{1/2}$	1.02±0.04‡	0.83±0.07*	1.09±0.07† 0.2 (0.1 to 0.4)

The mean difference from pre to post-ET is included with the 95% confidence interval (CI).Data are given as mean±SEM. MVC: maximum voluntary contraction; CSA: cross-sectional area; pH: pH = $-\log_{10}[H^+]$; [PCr]: phosphocreatine concentration; PCr $t_{1/2}$: phosphocreatine recovery half-time.

†Significantly different to pre-ET ($P<0.05$).

‡Close to 1 by definition.

*Significantly different from healthy control group ($P<0.05$).

function was poorer) in COPD subjects pre-training than in controls, but this difference was eliminated by training. The mitochondrial abnormality in individual subjects can be quantified by the ratio of the PCr $t_{1/2}$ predicted from end-exercise pH to that observed. As Table 2 shows, this is reduced by 19±8% in COPD subjects pre-training compared to controls ($P = 0.03$), and a significant improvement of 38±12% occurred with exercise training in the COPD subjects ($P = 0.007$) (Fig. 2B). There was also a significant increase in MVC and muscle CSA following exercise training (Fig. 2C).

Both the 6MWD and the peak workload on the cycle ergometer significantly increased in the COPD subjects following exercise training (Table 3). A correlation in peak workload with the ratio of the PCr $t_{1/2}$ predicted from end-exercise pH to that observed (i.e. measure of mitochondrial capacity) approached statistical significance ($r = 0.6, P = 0.07$).

Discussion

This study examined the effect of 16 sessions of endurance and strength exercise training, performed twice weekly, on exercise capacity as well as quadriceps mitochondrial capacity, strength and CSA in subjects with COPD. Muscle function in the COPD subjects prior to training was also compared to a group of healthy subjects matched for age and physical activity. Prior to exercise training, the COPD subjects had a lower mitochondrial capacity compared to the healthy controls, despite no

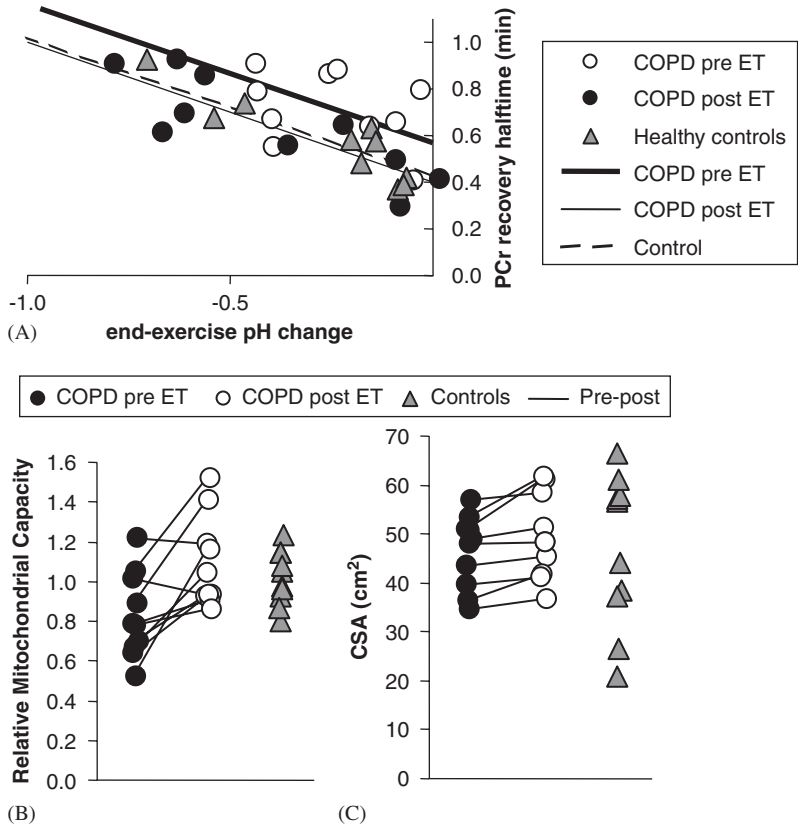

Figure 2 Results of muscle testing. (A) The relationship between PCr $t_{1/2}$ and end-exercise pH change in the subjects with COPD pre-exercise training (pre ET) and post-exercise training (post ET), and in the healthy control subjects: key to symbols is in the panel. Lines are fitted by grouped linear regression (see Methods): that for COPD pre-exercise training is significantly vertically shifted (see Results). (B) The relative mitochondrial capacity (derived from data in Fig. 2A: see Methods) in the subjects with COPD pre-exercise training (pre ET) and post-exercise training (post ET), and in the healthy control subjects: key to symbols is in the panel. Lines join pre- and post-exercise training data. Pre-exercise training mean in the subjects with COPD is significantly lower than control, and increases significantly pre- to post-exercise training (see Table 2). (C) Quadriceps CSA in the subjects with COPD pre-exercise training (pre ET) and post-exercise training (post ET), and in the healthy control subjects: key to symbols is in the panel. Lines join pre- and post-exercise training data. There was a significant increase from pre- to post-exercise training in the COPD subjects (see Table 2).

difference between groups in the size of the muscle. Following exercise training in the COPD subjects, exercise capacity as well as quadriceps mitochondrial capacity, CSA and strength all significantly increased.

Comparison of muscle function in COPD and health

As in other studies[29–31] there were no significant abnormalities in resting [PCr] or pH in the subjects with COPD. Thus the metabolic impairment in the COPD subjects was not sufficiently severe as to be unequal to the metabolic demands of the resting muscle. One way to further examine muscle mitochondrial capacity is to exercise the muscle sufficiently to cause [PCr] depletion and then observe the recovery of [PCr] once exercise stops.[32] There are several ways of doing this: the more intense the exercise the greater the PCr depletion achieved, and the better the precision of the crucial measurement of PCr $t_{1/2}$, but the associated pH fall makes the interpretation more difficult, and runs the risk of ATP depletion. Alternative approaches making use of the presumed causal relationships between, for example, rates of PCr resynthesis and [ADP][32] are difficult when ADP changes during exercise are relatively small, as they tend to be when pH changes are large. We have chosen an exercise protocol that produces adequate PCr depletion in subjects without excessive PCr depletion and ATP loss, and a method of data analysis that accounts for variable pH

Table 3 Six minute walk distance and the peak exercise response on the cycle ergometer in the COPD subjects ($n = 10$) before and after exercise training (ET)

	Pre-ET	Post-ET	Mean difference (95%CI)
Work			
Watts	46±5	53±4*	7 (2 to 12)
% predicted	41±5	48±4*	7 (1 to 12)
V_{O_2}			
L/min	0.81±0.10	0.85±0.04	0.04 (−0.07 to 0.1)
ml/kg/min	11.2±0.8	11.9±0.5	0.7 (−0.9 to 2.3)
% predicted	59±7	63±6	4 (−7 to 15)
V_{CO_2} (L/min)	0.84±0.1	0.88±0.1	0.05 (−0.1 to 0.2)
V_E (L/min)	32±3	34±2	2 (−3 to 7)
V_E/MVV (%)	98±9	94±6	−4 (−15 to 7)
V_t (L)	1.04±0.1	1.07±0.1	0.02 (−0.1 to 0.1)
f_b (brths/min)	32±2	33±2	2 (−1 to 4)
SpO_2 (%)	91±2	92±2	0.5 (−1 to 2)
HR (bpm)	117±8	114±6	−2 (−9 to 4)
HR (% pred)	72±5	70±4	−2 (−5 to 2)
Dyspnea	7±1	7±1	−0.1 (−2 to 1)
RPE	8±1	9±1	0.8 (−1 to 3)
6 MWD (m)	374±17	451±13*	77 (42 to 112)

Data are given as mean ± SEM. V_{O_2}: oxygen consumption; V_{CO_2}: carbon dioxide production; V_E: minute ventilation; V_E/MVV: ratio of minute ventilation to maximal voluntary ventilation; V_t: tidal volume; f_b: breathing frequency; SpO_2: oxygen saturation; HR: heart rate; RPE: rate of perceived exertion; 6 MWD: six minute walk distance.

*Significantly different to pre-ET ($P < 0.05$).

changes, and which can be used to quantitate abnormalities in functional mitochondrial capacity and changes produced by training.

Prior to exercise training in the COPD subjects, mitochondrial capacity was reduced compared to the healthy subjects. Previous studies have indicated similar results with an increased PCr $t_{1/2}$ in COPD subjects compared to healthy subjects.[15,30,31] However, two of these studies also noted a greater pH change with exercise in the COPD subjects[30,31] which makes the interpretation difficult.[29] In the present study, we allowed for pH change in our calculation, and infer a defect in mitochondrial function similar to that in a recent study.[15] In principle, this could be due to a reduction in mitochondrial volume, intrinsic mitochondrial defect or impaired oxygen supply because of arterial hypoxaemia or reduced capillary number. A previous study has shown that leg oxygen delivery at a given power output was not significantly different between COPD subjects and healthy subjects,[33] suggesting that impaired oxygen supply was not a factor. Previous studies of muscle oxidative enzymes[34–36] suggest that at least part of the functional defect is due to reduced mitochondrial number, volume or enzyme content.

The underlying aetiology for skeletal muscle dysfunction in COPD subjects has not been conclusively determined. Factors proposed to cause skeletal muscle dysfunction in COPD subjects include poor nutrition,[37] corticosteroid use,[38] systemic inflammatory processes,[39] hypoxia,[40] increased oxidative stress[3] and disuse.[41] Disuse is probably one of the primary reasons for the reduced quadriceps mitochondrial capacity prior to exercise training in the COPD subjects. When the disuse process was reversed by exercise training, quadriceps mitochondrial capacity improved. This will be discussed in the next section.

Changes with exercise training in COPD

From PCr recovery kinetics we infer a 38±12% increase in mitochondrial capacity from exercise training. Furthermore, quadriceps muscle CSA and MVC increased significantly (7±2% and 32±11%, respectively) in the COPD subjects following exercise training.

One other study has examined the effect of a continuous exercise training protocol on muscle metabolism using ^{31}P-MRS in COPD subjects.[15] Their results showed a significant improvement in PCr $t_{1/2}$ following 8 weeks of leg cycle training achieving values similar to healthy subjects. In that study, with small pH changes, this amounts to a 48±12% increase in mitochondrial capacity which is slightly, but probably not significantly, higher than in the

present work. One of the limitations of the work by Sala and colleagues[15] is that they recruited only male COPD subjects who had not had an exacerbation in the previous 6 months. This is not reflective of the usual COPD population attending pulmonary rehabilitation. Furthermore, the study used a tightly controlled training program of leg cycle exercise which differs from the comprehensive exercise training programs often used. The results of the current study add to the findings by Sala and colleagues[15] that improvement in quadriceps mitochondrial capacity is also possible in a comprehensive exercise training program for subjects (male and female) who attend pulmonary rehabilitation.

Another finding of our study was the significant improvement in 6MWD and peak work capacity on a cycle ergometer following training performed twice weekly. In contrast, Ringbaek et al.[42] have suggested that exercise training twice per week was not sufficient to show improvements in 6MWD. However, the description of the training component used in their study was limited with intensity based on dyspnea levels and the duration of endurance training (jogging and stair-climbing) not cited. In our study, an extensive endurance training component was prescribed (30 min of walking and 20–30 min of cycling by week 8) with intensity based on the 6 min walk test and cycle ergometer test. The trend towards a significant correlation between the increase in peak leg work capacity and the improvement in mitochondrial function provides some evidence that the improvement in peak exercise capacity was related to the physiological changes at the skeletal muscle level after training.

The findings of this study were limited by factors which warrant some caution in data interpretation. The small sample size may have limited the ability to distinguish between the COPD and healthy subjects particularly in regard to baseline muscle strength. We recognise that a number of studies have detected differences in muscle strength and CSA between healthy and COPD subjects.[3,11] However, our healthy control group was sedentary and slightly older than subjects in these studies which may have minimised the differences between the healthy and COPD subjects in our study. In addition, as there was no COPD control group, the effect of exercise training on the muscle changes occurring in the COPD subjects will need to be confirmed in a randomised controlled trial.

In conclusion, 16 sessions of exercise training, performed twice weekly, significantly increased 6MWD and peak leg work capacity in the subjects with COPD. There was a significant improvement in [PCr] resynthesis kinetics of the quadriceps muscle suggesting an improvement in the oxidative capacity of the muscle. Quadriceps muscle mass and strength also significantly increased following twice weekly training.

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Competing interest statement

The authors wish to declare no competing interests with respect to this work.

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